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BEHAVIOR AND PHYSIOLOGY OF THE MONKEY (MACACA MULATTA) FOLLOWING 2500 RADS OF PULSED MIXED GAMMA-NEUTRON RADIATION

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ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

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BEHAVIOR AND PHYSIOLOGY OF THE MONKEY (MACACA MULATTA) FOLLOWING 2500 RADS OF PULSED MIXED GAMMA-NEUTRON RADIATION

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TABLE OF CONTENTS

	Page
Foreword (Nontechnical summary)	iii
Abstract	v
I. Introduction	1
II. Materials and Methods	1
III. Results	4
IV. Discussion	11
References	14

LIST OF FIGURES

Figure 1. Behavior and physiology following irradiation	6
Figure 2. Behavior and physiology following irradiation	6
Figure 3. Behavior and physiology following irradiation	7
Figure 4. Behavior and physiology following irradiation	7
Figure 5. Behavior and physiology following irradiation	8
Figure 6. Behavior and physiology following irradiation	8
Figure 7. Mean values for behavior and physiology of six monkeys irradiated with 2500 rads midline tissue dose of mixed gamma-neutron radiation	10

TABLE

Table I. Aortic Pressure at the Beginning and End of the Early Performance Decrement Period	9

FOREWORD
(Nontechnical summary)

In the present study, monkeys were trained to perform a shock motivated visual discrimination task. These monkeys were then surgically implanted to monitor aortic and venous pressures, carotid flow, heart rate and respiratory rate. These physiological indices were monitored before and following irradiation to evaluate the effects of physiological changes on the monkey's ability to perform a learned task.

Five of six animals showed a performance decrement (less than 90 percent correct responses) within the first 10 trials (1.67 minutes) of the first 100-trial session (16.7 minutes) following irradiation. One animal displayed no decrement in performance during this first session. All of the animals except one performed at an acceptable level (above 90 percent correct responses) after the performance decrement during the first session. Five of the animals showed a second decrease in performance between 40 and 45 minutes postirradiation. The performance of four animals returned to an acceptable level following this secondary performance decrement.

The aortic pressure was severely decreased in five of six animals from approximately 8 to 20 minutes postirradiation. The first physiological indication of the ensuing incapacitation was an increase in pulse pressure caused by a rapid decrease in diastolic pressure quickly followed by a decrease in systolic pressure. Performance was not adversely affected until the diastolic pressure decreased to approximately 35 mm Hg. The systolic pressure varied considerably at this time

from animal to animal. A return to acceptable performance levels did not occur until the aortic pressure returned to approximately 80/40 mm Hg.

The respiration rate was generally increased postirradiation. The heart rate increased significantly during the third session (63-80 minutes postirradiation). No significant changes were observed in the carotid flow or venous pressure.

The possible mechanisms which control the physiological indices monitored and the changes in these mechanisms as they relate to behavior are discussed.

ABSTRACT

Six monkeys, which had been trained to perform a shock motivated visual discrimination task, and which had been surgically implanted to monitor aortic and venous pressures, carotid flow, heart rate and respiratory rate were irradiated with a 2500-rad midline tissue dose of mixed gamma-neutron radiation. Four of the six animals displayed an early performance decrement (less than 90 percent correct responses) within a few minutes following irradiation. One animal showed no performance decrement, and one animal made only five responses and then ceased to perform at all following irradiation. Animals which displayed a performance decrement suffered an acute decrease in aortic pressure. The first physiological indication of the ensuing incapacitation period was a rapid fall of diastolic pressure followed by a decrease in systolic pressure. A second period of behavioral decrement was observed in five of the six animals at approximately 40-45 minutes post-irradiation. The respiratory rate was, in general, significantly increased following irradiation. No significant changes were observed in carotid flow or venous pressure.

I. INTRODUCTION

Other investigators have reported that a monkey trained for a shock motivated visual discrimination task will usually fail to perform at acceptable levels within minutes after receiving a 2500-rad midline tissue dose (MTD) of mixed gamma-neutron radiation.[4,5] This performance decrement is most severe from 5 to 20 minutes following irradiation and has been referred to as the early transient incapacitation (ETI) period.[9] In another investigation utilizing untrained monkeys it has been reported that the aortic pressure is greatly decreased in a similar time frame (5-20 minutes) postirradiation.[12] It has also been reported that the carotid flow decreases as the aortic pressure decreases following irradiation in partially anesthetized monkeys.[1]

Previous investigations have concentrated on collecting either behavioral or physiological data;[1,4,9,12] few comprehensive studies have been done that have related both behavioral and physiological indices. In the present study, the relationship between physiological changes and behavior following irradiation was studied.

II. MATERIALS AND METHODS

Six young adult male monkeys (Macaca mulatta) weighing between 3 and 5 kg were utilized in this study. The animals were maintained in primate chairs and housed in individual isolation cubicles.

The monkeys were trained to perform a simultaneous visual discrimination task using shock motivation. The apparatus and training procedures have been previously described.[2] Trials were presented at 10-second intervals, with the

animal given 5 seconds to respond to the correct key. If the animal failed to respond within 5 seconds or made an incorrect response, it received a brief electrical shock. Trials were presented in a series of 100 trials (16.7 minutes), and each series was followed by a 15-minute rest period. During the training period of approximately 25 days, the animals remained in the primate chairs. When each animal achieved an overall proficiency of 90 percent or greater correct responses per 100 trials on the behavioral problems, they were surgically implanted with physiological monitoring devices. The surgical procedure consisted of placing catheters into the femoral artery and vein and then advancing the respective catheters into the aorta and vena cava; a flow transducer* and vessel occluder† were placed on the left common carotid artery. Surgery was performed approximately 2 weeks before irradiation. Two days before irradiation each animal was tested for 4 hours on the visual discrimination task. Correct responses of 90 percent or better were considered as an acceptable level of performance. An animal which did not maintain an acceptable level of performance throughout the preirradiation testing period was removed from the study. During the preirradiation testing, all physiological and behavioral indices were continuously monitored.

Food was withheld from the monkeys for 16 hours before irradiation; however, water was available ad libitum except for a period of approximately 3 hours. This 3-hour period without water included preparation of the animal and the time spent in the exposure room. Approximately 90 minutes before irradiation, the animals were

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* Flow transducer BL5020, Biotronex Laboratory Inc., Silver Spring, Maryland

† Blood vessel occluder, Model VL-3, In Vivo Metric Systems, Los Angeles, California

transported to the exposure room and placed in an isolation cubicle. The arterial and venous catheters were connected to pressure transducers,* and the blood flow transducer was connected to the flowmeter.† The output of the transducers and flowmeter was recorded using a Sanborn‡ recorder.

The monkeys were positioned in the exposure room of the AFRRI-TRIGA reactor to receive a calculated dose of 2500 rads. The midline tissue dose (MTD) was obtained by determining the tissue kerma, free-in-air, at the midline exposure volume and multiplying this value by an experimentally derived factor (0.85). For these exposures the operation of the reactor and the characteristics of the radiation field were as previously described.[3]

Before irradiation the animals were given two sessions of 100 trials with a 15-minute rest period following each session. The pulse of radiation was received by the animals at the end of the second rest period. This schedule (100 trials plus 15-minute rest period) was continued following irradiation for approximately 2 hours or four sessions. After the first 2 hours the animals were tested for one session each hour until 6 hours postirradiation and then tested at 4-hour intervals until death.

The behavioral data were tabulated at 10-trial intervals with the physiological data being taken at the end of each 10-trial period. The physiological indices were also tabulated at 2 and 10 minutes during the 15-minute rest periods. The physiological data were statistically analyzed using the analysis of variance with a one-way

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* Pressure transducers: arterial, Type P23Db; venous, Type P23BB, Statham Laboratories Inc., Hato Rey, Puerto Rico

† Flowmeter Model B1-610, Biotronex Laboratory Inc., Silver Spring, Maryland

‡ Eight-channel recorder, Model 7700, Hewlett-Packard Co., Rockville, Maryland

layout for equal or unequal group size.[11] Values were considered significantly different when $p < .05$.

III. RESULTS

The behavioral performance and physiological indices which showed a significant change during the ETI period are presented for each animal in Figures 1-6. Mean values for performance and all physiological indices monitored in the study are presented in Figure 7.

Five of the six animals showed a performance decrement early in the first session of 100 trials following irradiation (Figures 1-3, 5 and 6). This behavioral decrement was evident within the first block of 10 trials. All animals except one were not responding by the ninth trial of the first session (Table I). The animal showing no early performance decrement is presented in Figure 4. Of the animals experiencing the early performance decrement, all except one (Figure 5) performed at an acceptable level during at least one of the 10-trial blocks in the first session.

Three of the animals were performing at an acceptable level at the beginning of the second session (Figures 1-3). All five animals that were performing at the beginning of the second behavioral session appeared to display a performance decrement between 40 and 45 minutes postirradiation. Four of these animals performed at an acceptable level following the second performance decrement in the second session. However, only two of the six animals (Figures 1 and 2) were performing at an acceptable level by the fourth session following irradiation.

The latency of response tended to increase as the correct responses of the animals decreased. No increase in latency with time postirradiation for the four sessions monitored following irradiation was noted when the animals were performing at an acceptable level.

Aortic pressure was significantly decreased in the five animals displaying a performance decrement during the first session following irradiation. This decreased aortic pressure lasted from 8 to 20 minutes postirradiation before returning toward preirradiation levels; however, the aortic pressure never returned to preirradiation values. In one animal (Figure 4), no decrease in aortic pressure was observed during the first session following irradiation. The aortic pressure in this animal remained at near normal values during the first session and then decreased slowly during subsequent sessions.

The first physiological indication of the ensuing ETI was an initial decline in diastolic pressure followed by a decrease in systolic pressure. This decrease in both systolic and diastolic pressures resulted in a lowered pulse pressure during the ETI period (Figures 1-3, 5 and 6). The initial fall in diastolic pressure occurred while the animal was performing at acceptable levels. Behavioral performance was not adversely affected until the diastolic pressure was approximately 35 mm Hg. Correct behavioral responses ceased after the eighth or ninth trial of the first session for those monkeys that experienced an initial performance decrement. When the aortic pressure returned to approximately 80/40 mm Hg, behavioral performance resumed in four of the five monkeys that suffered the initial performance decrement (Table I).

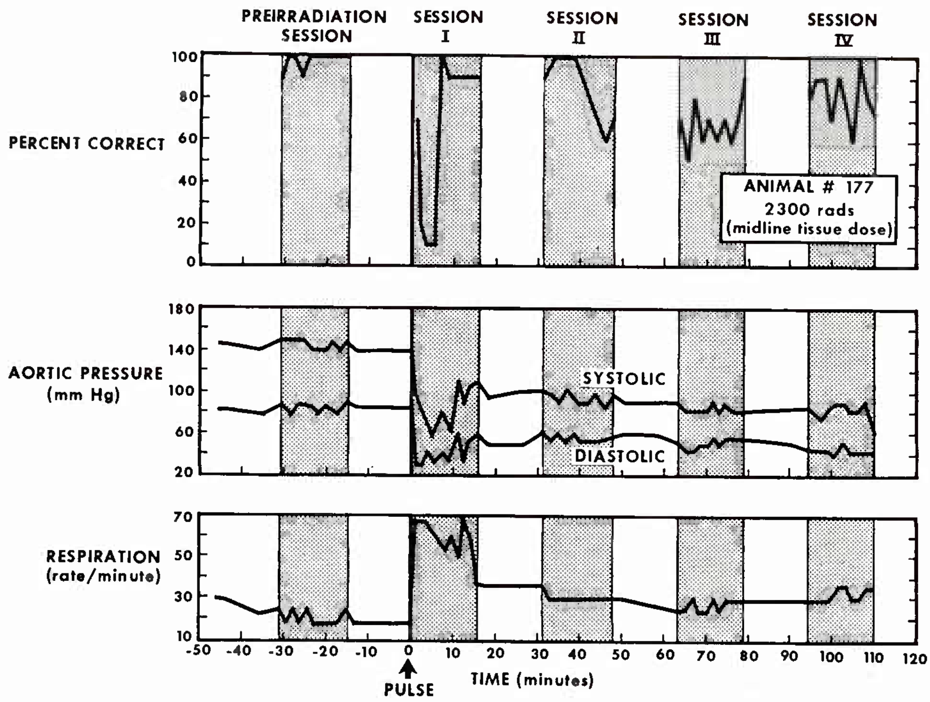

Figure 1. Behavior and physiology following irradiation

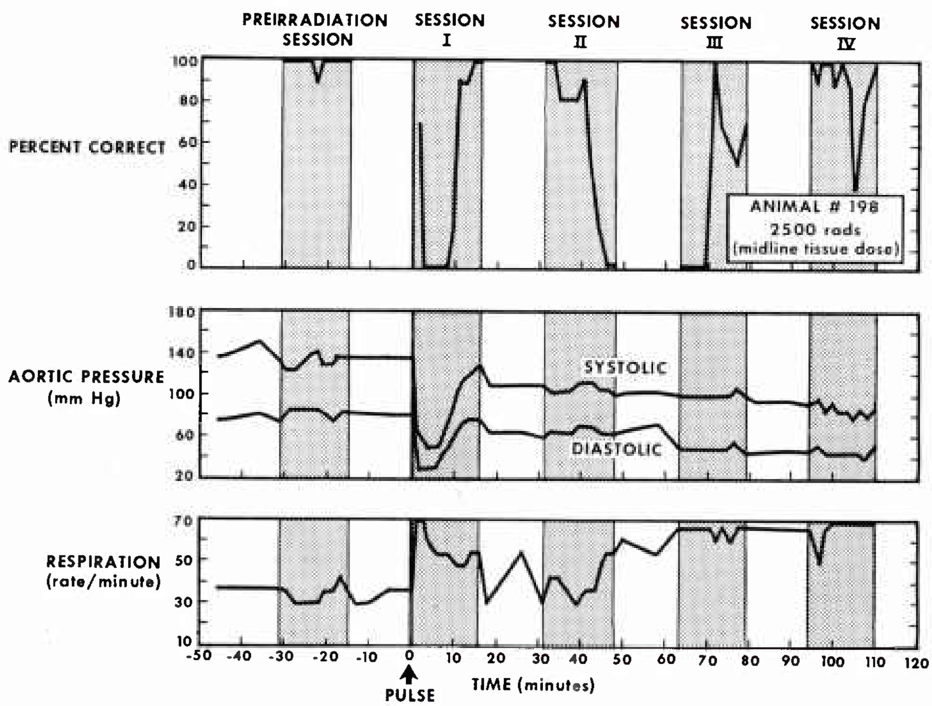

Figure 2. Behavior and physiology following irradiation

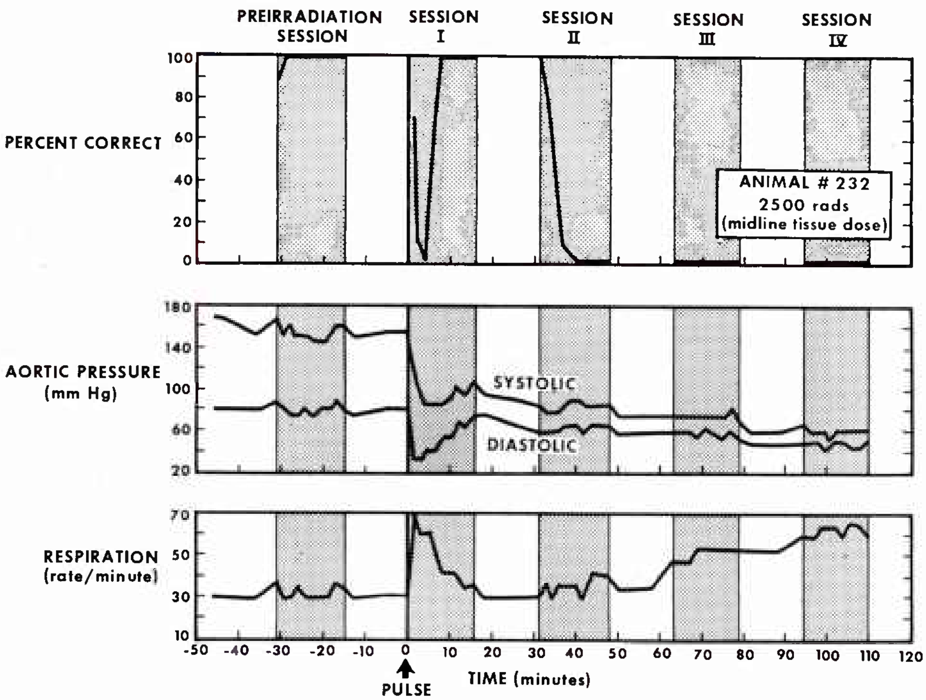

Figure 3. Behavior and physiology following irradiation

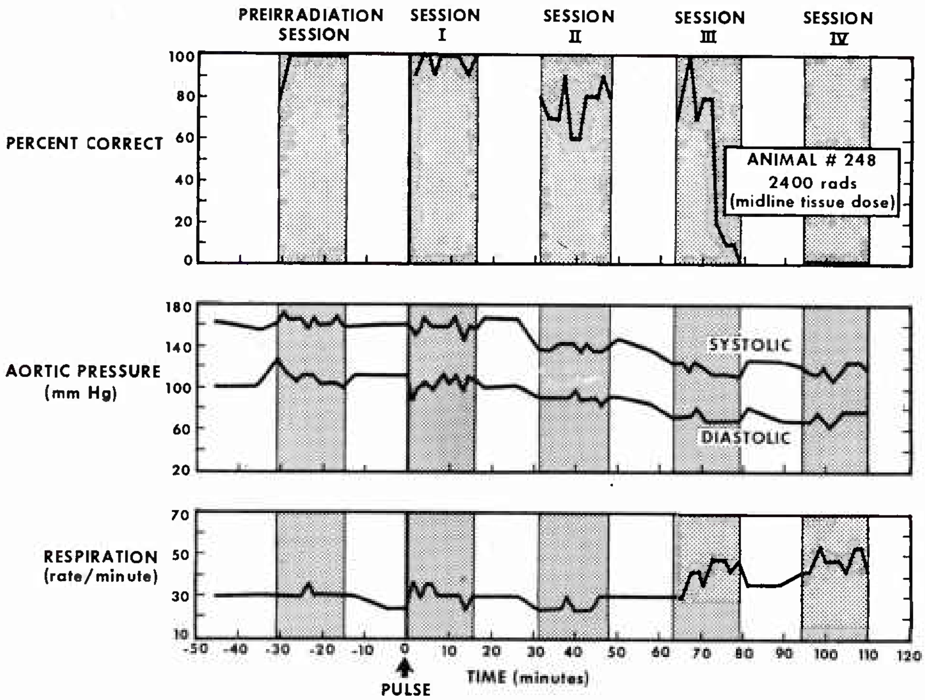

Figure 4. Behavior and physiology following irradiation

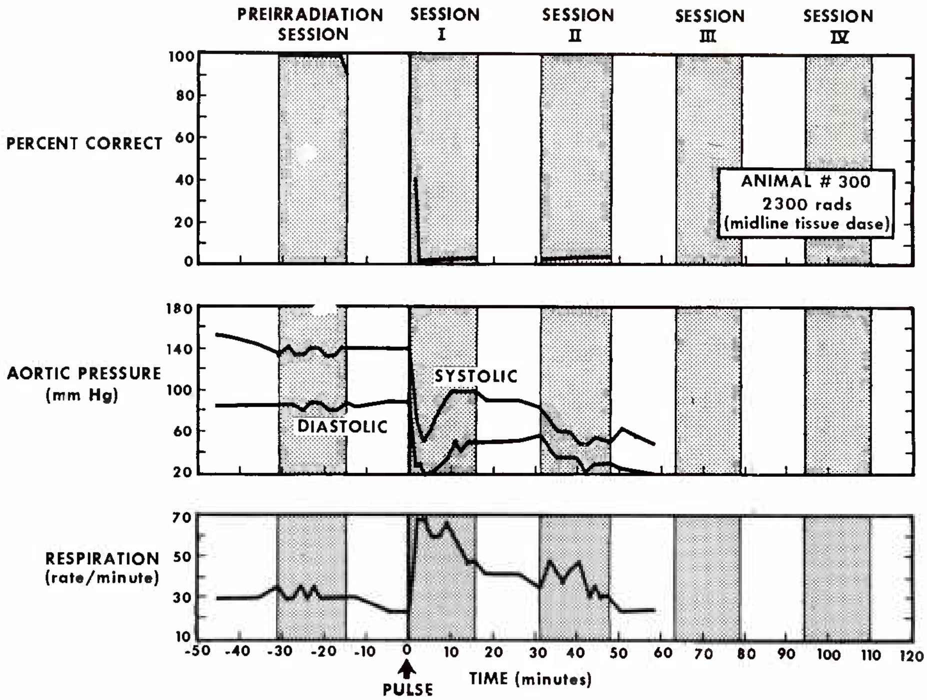

Figure 5. Behavior and physiology following irradiation

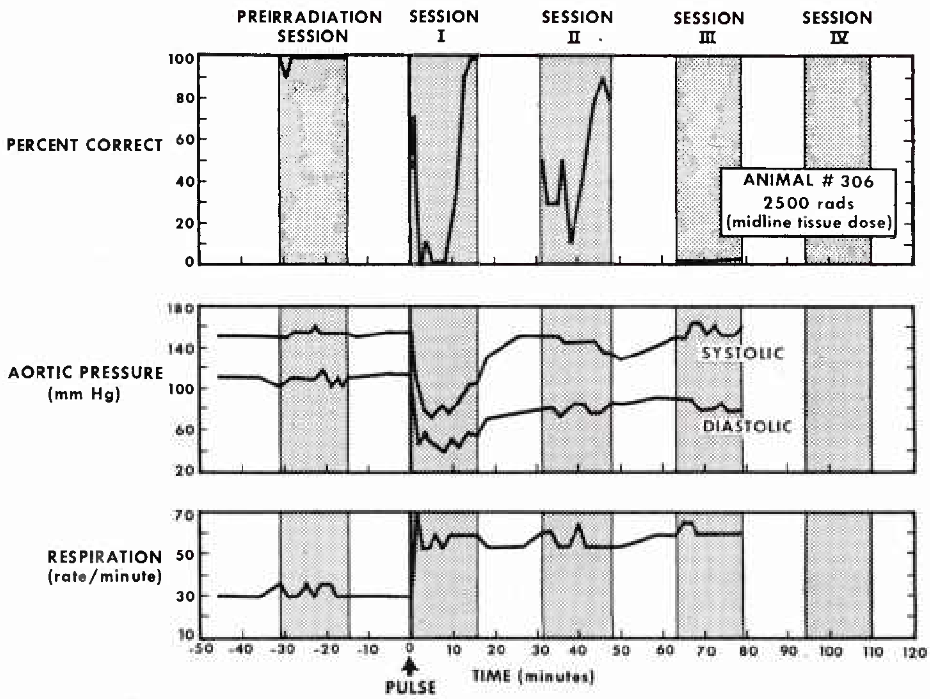

Figure 6. Behavior and physiology following irradiation

Table I. Aortic Pressure at the Beginning and End of the Early Performance Decrement Period

Animal #	Preirradiation pressure systolic/diastolic (mm Hg)	Beginning of omissions first session (trial number)	Aortic pressure at first omission systolic/diastolic (mm Hg)	Aortic pressure when correct responses resumed systolic/diastolic (mm Hg)
177	140/85	9	100/30	80/35
198	135/80	8	68/25	83/45
232	155/80	9	115/35	80/40
248	160/100	--	--	--
300	140/85	5	90/20	--
306	150/110	8	130/45	85/50

The respiratory rate was significantly increased in those animals that displayed both a performance decrement and a decreased aortic pressure. This increased respiratory rate was especially evident during the ETI period of the first session (Figures 1-3, 5 and 6). The respiratory rate remained elevated following irradiation except during the first and second rest periods and the second behavioral session. One animal (Figure 4) showed no initial ETI and exhibited no increase in respiratory rate until permanent complete incapacitation (PCI) occurred during the third session following irradiation.

A significant increase in heart rate was observed during the third session following irradiation, and the heart rate tended to increase gradually through the 2nd hour postirradiation (Figure 7). During the period of observation, no significant changes were observed in either common carotid flow or venous pressure.

The mean survival time of the animals following irradiation was 14.5 hours with a range of 1.5 to 29 hours.

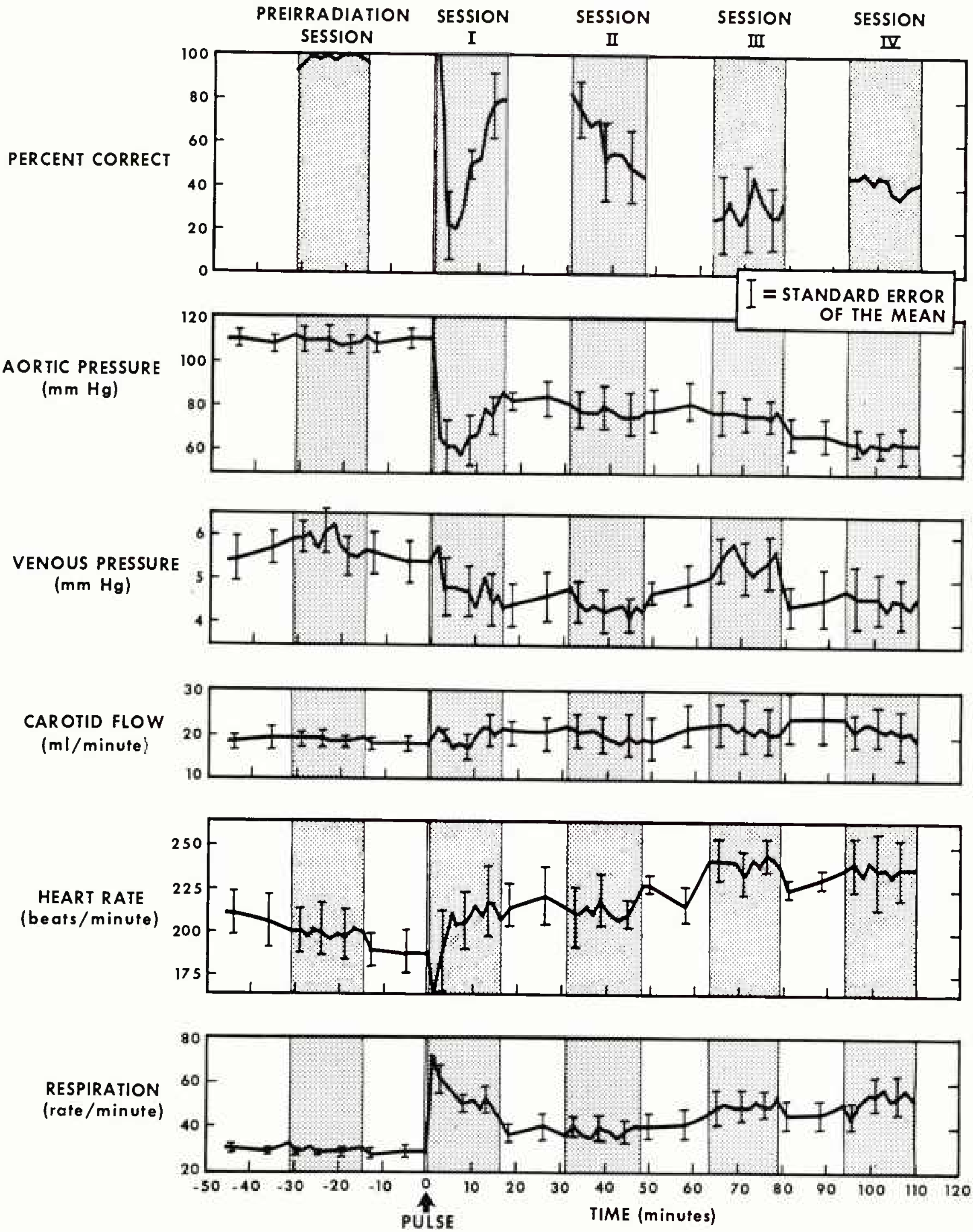

Figure 7. Mean values for behavior and physiology of six monkeys irradiated with 2500 rads midline tissue dose of mixed gamma-neutron radiation

IV. DISCUSSION

Five of the six animals used in this study experienced a period of behavioral decrement within a few minutes postirradiation. During this period, the animals were unable to perform a learned task, their aortic pressure decreased acutely, and an increase in respiration rate occurred. No significant change was observed in the common carotid flow, venous pressure or heart rate during the ETI period.

The first physiological indication of the ensuing ETI period appears to be a rapid decrease in diastolic pressure followed by a fall in systolic pressure. Initially the pulse pressure is increased mainly by the fall in diastolic pressure. A more gradual decline in systolic pressure then occurs resulting in a decreased pulse pressure and a lowered mean aortic pressure during the ETI period (Figures 1-3, 5 and 6). This decrease in diastolic pressure is probably caused by damping due to dilation of the arteriole beds. Dilation of the arteriole beds would alter the resiliency of the vessels and the diastolic pressure would decrease. As the arterioles and larger arteries become dilated or relaxed, a drop in systolic pressure would occur as the summation or reflected pressure waves were reduced.

The decrease in aortic pressure during ETI has been prevented with the use of compounds such as norepinephrine or 2-(n-decylamino) ethanethiosulfuric acid (1607).[*,6,8,10] Workers in this laboratory have maintained aortic pressure for a period following irradiation with the continuous infusion of norepinephrine. However, when the infusion of norepinephrine was halted the aortic pressure decreased

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* Unpublished: Turbyfill, C. L., Roudon, R. M. and McFarland, W. L., Armed Forces Radiobiology Research Institute, Bethesda, Maryland

acutely.[8] Other work at the AFRRI has shown that compound 1607 will maintain the aortic pressure when injected intravenously 30 minutes before irradiation (10 mg/kg), and it greatly enhances the monkey's ability to perform following irradiation.* Thus, the use of certain compounds (norepinephrine and 1607) can maintain the aortic pressure during the ETI period.

The time when the aortic pressure decreases coincides with the decrement in behavioral performance. However, it appears that the change in aortic pressure may not be the major contributor to behavioral incapacitation, since it has been shown at this laboratory that maintaining aortic pressure with norepinephrine does not have a beneficial effect on postirradiation performance.+ The authors speculate that 1607 is able to enhance both behavioral and physiological indices by its action on the vasculature of the brain and that the maintenance of systemic blood pressure by this compound is of secondary importance.

In the present study, the flow within the common carotid did not significantly change following irradiation. Chapman and Young, employing partially anesthetized animals irradiated soon after surgery, found that both the aortic pressure and internal carotid flow decreased following irradiation.[1] From the results in the present study, it appears that blood flow to the brain is maintained during ETI. However, slow EEG waveforms have been recorded by surface electrodes during this period.[7] These changes in EEG waveforms may indicate a reduction or shunting of blood flow from the cortical areas of the brain.

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* See footnote on page 11

\+ Unpublished: Turns, J. E. and Curran, C. R., Armed Forces Radiobiology Research Institute, Bethesda, Maryland

The immediate increase of the respiratory rate in animals experiencing ETI may also indicate an alteration of the cerebral flow pattern. If areas of the brain are hypoxic due to an altered circulatory pattern, then the concentration of carbon dioxide would increase and stimulate the chemoreceptors of the medulla oblongata. It does not appear that the concentration of carbon dioxide would reach a level which would initiate the increase noted in the respiratory rate immediately following irradiation. The respiration rate also increases in later sessions when the monkey's behavioral performance level decreases. This latter increase could possibly be initiated by the animal receiving electrical shock for failure to respond to the behavioral problem.

The survival time for the animals used in this study appears to be somewhat less than that observed in comparable studies utilizing animals not subjected to surgical stress.[4] The explanation for this apparent difference has not been adequately defined, but the symptomatology and behavioral performance appear similar for the 1st hour postirradiation for both intact monkeys and those monkeys subjected to surgery.[4,12]

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13. ABSTRACT

Six monkeys, which had been trained to perform a shock motivated visual discrimination task, and which had been surgically implanted to monitor aortic and venous pressures, carotid flow, heart rate and respiratory rate were irradiated with a 2500-rad midline tissue dose of mixed gamma-neutron radiation. Four of the six animals displayed an early performance decrement (less than 90 percent correct responses) within a few minutes following irradiation. One animal showed no performance decrement, and one animal made only five responses and then ceased to perform at all following irradiation. Animals which displayed a performance decrement suffered an acute decrease in aortic pressure. The first physiological indication of the ensuing incapacitation period was a rapid fall of diastolic pressure followed by a decrease in systolic pressure. A second period of behavioral decrement was observed in five of the six animals at approximately 40-45 minutes postirradiation. The respiratory rate was, in general, significantly increased following irradiation. No significant changes were observed in carotid flow or venous pressure.

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